CHANGES IN INGESTIVE CAPACITY OF MACROPHAGES FROM DIFFERENT ORGANS IN RESPONSE TO HYDROCORTISONE

D. N. Mayanskii, N. P. Voronina, and A. Yu. Voronin

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Glucocorticoids modify recognition of objects of phagocytosis [8], their elimination [2], conjugation of lysosomal membranes with the phagosome [4], and the bactericidal [15] and secretory [14] functions of macrophages (M). Meanwhile, the M population is distinguished by extreme heterogeneity. To begin with, resident M differ from M from the wandering pool. For instance, Kupffer cells (KC) are aimed more at ingesting foreign particles, including denatured autologous erythrocytes, latex particles, colloidal particles of carbon, iron, and so on. At the same time, M from the alveolar space ingest erythrocytes less actively, but phagocytose *Mycobacterium tuberculosis* cells more effectively [6]. M from the peritoneal cavity are distinguished by the high density of their Fc- and C_3-receptors, by a high percentage of Ia^+ cells, and for that reason, they are more actively involved in reactions of specific immunity than KC [7]. Resident M from different organs evidently also differ in functional activity, although this is a question for special study. In support of interorgan differences between resident M there is some evidence, such as their different ability to ingest foreign particles both through immune [7] and through nonspecific binding mechanisms [11]. In all probability this difference should also extend to the sensitivity of M for hydrocortisone (HC).

The aim of this investigation was to study changes in the ingestive capacity of resident M from different organs of the reticuloendothelial system (RES) after a single injection of a pharmacologic dose of HC.

EXPERIMENTAL METHOD

Experiments were carried out on 120 female Wistar rats weighing 240-280 g and on 35 female CBA mice weighing 20-25 g. There were three series of experiments altogether. In series I HC acetate (from Richter, Hungary) was injected intraperitoneally in a dose of 125 mg/kg body weight. The rate of clearance of the blood from colloidal carbon particles (from Günther Wagner, West Germany) was determined 1 and 3 weeks after injection of the hormone and expressed as the value of K indices [2]. Pieces of liver from the central regions of the right lobe were fixed in neutral 10% formalin and Carnoy's fluid. The number of KC in 1000 hepatocytes and the percentage of KC loaded with carbon particles were determined in sections 4-5 μ thick, stained with hematoxylin and eosin. At the same time the number of monocytes was counted in the blood. The plasma 11-hydroxycorticosteroid (11-OHCS) level was determined by Specol (East Germany) spectrofluorometer [3].

In the experiments of series II, mice were given an intravenous injection of 10^8 sheep's red blood cells (SRBC), labeled with ^{51}Cr (^{51}Cr-SRBC) 2, 24, and 72 h after injection of 125 mg/kg of HC. The SRBC were incubated with $Na_2{}^{51}Cr_2O_5$ for 2 h at 37°C with constant shaking. The labeled SRBC were washed three times with medium 199 at 3000 rpm for 10 min. Blood samples measuring 0.1 ml were taken from the retro-orbital sinus, 20-30 sec and 3, 6, and 15 min after injection of ^{51}Cr-SRBC, in order to determine the K indices. The animals were killed 1 h later. Radioactivity was measured in the liver, lung, spleen, bone marrow (BM), and kidney, by means of a Tesla automatic Gamma-counter (Czechoslovakia). The distribution of radioactivity between the organs (%P), and the percentage of injected dose of ^{51}Cr-SRBC, calculated relative

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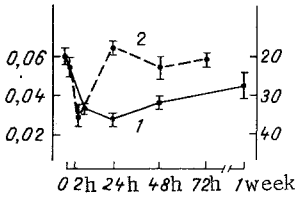

Fig. 1

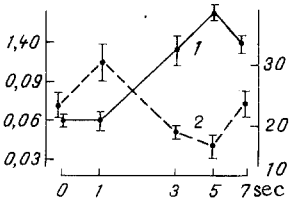

Fig. 2

Fig. 1. K indices (1) and plasma 11-OHCS level (2) after injection of 125 mg/kg of HC into rats (M ± m). Here and in Fig. 2: abscissa, time of investigation; ordinate: on left — value of K index (in min^{-1}), on right — 11-OHCS concentration (in μg%).

Fig. 2. K indices and plasma 11-OHCS level in rats after injection of 100 mg/kg of zymosan granules (M ± m).

TABLE 1. Effect of HC on Uptake of ^{51}Cr-SRBC by Various Organs of CBA Mice (M ± m)

Organ	Parameter	Control (n = 12)	Time after injection of HC, h		
			2 (n=7)	24 (n=9)	72 (n=6)
Liver	%O	65,0±3,1	49,3±4,5 P<0,01	47,7±3,9 P<0,01	37,2±1.8 P<0,001
	%T	54,3±3,6	43,4±4,1	36,0±3,1 P<0,01	28,9±1.8 P<0,001
	%P	86,2±1,7	83,7±1,9	83,4±1,2	82,5±1,2
Lung	%O	3,7±0,3	3,6±0,4	3,8±0,5	3,4±0,3
	%T	25,9±1,7	25,3±3,8	29,7±3,2	33,8±4,3
	%P	4,9±0,4	6,0±0,6	6,3±0,9 P<0,05	7,5±0,5 P<0,01
Spleen	%O	4,9±0,8	5,0±0,7	4.9±0,7	2,9±0,3 P<0,05
	%T	60,8±8,6	76,4±10,6	86,7±10,2	87,8±9.4 P<0,05
	%P	6,3±0,9	9,5±1,1 P<0,05	8,1±1,1	7,9±0,9
Bone marrow	%O	0,4±0,04	0,4±0.07	0,6±0,09 P<0,05	0.9±0,01 P<0,001
	%P	0,4±0,01	0,5±0,1	0,7±0,1 P<0,05	1,9±0,2 P<0,001
Kidney	%O	0,6±0,006	0,8±0,2	0,3±0,2	0.7±0.1
	%T	5,3±0,6	7,9±1,5	3,2±0,3 P<0,05	5.3±1,1
	%P	1,1±0,8	1.3±0,2	0.8±0.009	1.5±0,3

to the weight of the organ (%O) and per gram weight of its tissue (%T) were calculated from the readings of the counter.

In the experiments of series III, to stimulate the RES the rats were given an intravenous injection of zymosan granules (ZG) in a dose of 100 μg/kg body weight (from Reakhim, USSR). The rate of clearance of the blood from colloidal carbon and the plasma 11-OHCS level were determined 1, 3, 5, and 7 days after injection of ZG. The data were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

By 2 h after injection of HC into the rats the rate of clearance of the blood from colloidal carbon was reduced by more than half. This was observed 24-48 h after injection of HC. Depression of the clearing function of the RES took place mainly on account of a decrease in phagocytic power of the macrophages of the liver: in the control, particles of colloid were ingested by 74.0 ± 2.5% of KC, but 24 h after injection of HC, by only 52.4 ± 3.5%. The number of monocytes in the peripheral blood was reduced by one-third 24 h after injection of the hormone. The rate of clearance of the blood from colloidal carbon was partly restored to normal 1 week after injection of HC, but not until 3 weeks after the injection was recovery complete (Fig. 1). The plasma 11-OHCS level was significantly increased only after 2 h, and at all other times of the investigation it was the same as in the control (Fig. 1).

In mice 2 h after injection of HC a tendency was observed for the K index to fall, and the rate of clearance of the blood from ^{51}Cr-SRBC was reduced after 24 and 72 h by 2.2 and 1.7

times, respectively, compared with the control. Depression of the ingestive power of the RES was due mainly to a decrease in uptake of ^{51}Cr-SRBC by liver macrophages. This was observed as early as 2 h after injection of HC. The ingestive capacity of the liver M was depressed even more after 24 and 72 h. As regards the pulmonary M, their ingestive power 2 h after injection of HC showed no significant change, whereas after 24 and 72 h the %T index showed a tendency to rise, whereas %P was significantly higher than in the control. Analysis of the splenic component of RES revealed a tendency for the values of %T and %P to rise 2 and 24 h after injection of HC, but after 72 h the uptake of ^{51}Cr-SRBC by the whole organ (%O) was significantly reduced. Meanwhile, in connection with the reduction in weight of the spleen after loading with HC, %T remained higher than in the control. Incorporation of ^{51}Cr-SRBC into BM 2 h after injection of HC was virtually indistinguishable from the control. However, after 24 h, and, in particular, after 72 h, values of %O and %P were significantly higher than in the control. Total radioactivity in the whole kidney (%O) after injection of HC differed only a little from the control, whereas the value of %T was significantly lower after 24 h than in the control (Table 1).

The 11-OHCS level in the blood 24 h after injection of ZG did not differ significantly from the control values, although it had a tendency to rise, and by the 3rd day and, in particular, by the 5th day, during the period of maximal acceleration of clearance of the blood from colloidal carbon particles, the 11-OHCS level was significantly lower than in the control (Fig. 2).

These results indicate that the sensitivity of resident M from different organs to HC differs. Consequently, it must be noted that in hemorrhagic shock [9], starvation [5], and burns [10] the ingestive function of the KC is depressed by a considerable degree, whereas clearance of the blood through resident M in the lung and spleen may actually be intensified in these situations. The high sensitivity of KC to the clearance-inhibiting effects of HC may arise for different reasons. In particular, the density of receptors for HC on KC may be higher than on other classes of M. Glucocorticoids stabilize the outer membranes of M and thus inhibit ingestion and subsequent stages of conjugation of lysosomal membranes with the phagosome [1]. The possibility cannot be ruled out that synthesis of fibronectin, which is a universal opsonin, to a deficiency of which KC are particularly sensitive [13], is inhibited under the influence of HC. KC participate in the early stages of HC metabolism [12]. According to our data, at the peak of stimulation of RES the blood 11-OHCS level was sharply reduced. This could be associated with acceleration of metabolism of glucocorticoids in cells of the RES in the liver after their stimulation. It may therefore be possible to modify significantly hormone-dependent metabolic changes in different versions of acute stress and in the course of long-term adaptation, through modulation of reactivity of Kupffer cells and of the RES as a whole.

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